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April 1, 2002

Catherine M. DeRozver
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

Dear Ms. DeRozver,

The topics to be discussed at the meeting of the Food Advisory Committee to be held on April 4 and 5, 2002 are of considerable importance with respect to evaluation of the efficacy and safety of "quality factors" added to infant formulas. Moreover, this topic is likely to become even more important as means of adding a variety of factors present in human milk to formulas are perfected. Examples that come to mind immediately include a variety of pre and probiotics, lactoferrin and other specialized proteins, a variety of enzymes and long-chain polyunsaturated fatty acids. Further, the scientific principles that must be applied in evaluation of the efficacy and safety of these "quality" factors are likely to be different for each factor.

In this regard, I have been involved for the past few years in the controversy of whether long chain polyunsaturated fatty acids (LC-PUFA), which are present in human milk, should be added to infant formulas. How my views have changed and the factors responsible for these changes may be of interest to the Committee as it tackles the assigned topics. For this reason, I have decided to respond to the invitation to provide a written submission.

I began my involvement in this area as a skeptic. Although the theoretical reasons for including LC-PUFAs in infant formulas were strong, the limited outcome data available in the early 1990s, when I became interested in this area, were not convincing. More important, there were a number of safety issues, most related to the known biological effects of LC-PUFA, that had not been resolved. Thus, while many argued that formula-fed American infants were being deprived of a vital nutrient, I argued that addition of this nutrient to formulas should await further evaluation of the legitimate safety concerns.

Currently, the data for the efficacy of formulas supplemented with LC-PUFA are somewhat more convincing but still not overwhelming. Moreover, few of the specific safety issues outlined earlier (Heird, WC. Biological effects and safety issues related to long-chain polyunsaturated fatty acids in infants. *Lipids* 1999; 34:207-214) have been addressed directly. On the other hand, a number of large studies in preterm infants have shown absolutely no difference in incidence of diseases that might result from the specific safety concerns between infants receiving conventional preterm formula *vs.* the same formula supplemented with LC-PUFA. I'm still not totally convinced of the efficacy of supplementing term or preterm formula with LC-PUFA. However, I no longer have

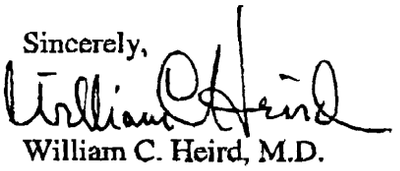
doubts about the safety of these fatty acids for either preterm or term infants when used in the same form and the same amounts as in the studies described above.

In this regard, I altered my views about the safety of both preterm and term formulas containing LC-PUFA on the basis of safety data in preterm infants. Hence, while I don't think it is possible in all instances to generalize findings from a clinical study using preterm infant formula consumed by preterm infants to a term infant formula intended for use by term infants, I obviously think it is possible in some instances. With respect to such generalization of safety data, I can think of no physiological system that is not more vulnerable to safety issues in the preterm than in the term infant. Thus, if this is the case, I feel comfortable concluding that a quality factor evaluated in preterm infants as a component of preterm formula and found to be "safe" is likely to be equally safe (or more so) as a component of term formulas intended for term infants. This is particularly true if the amount of the factor to be added to the term formula is not more than the amount studied in preterm infants as a component of preterm formulas.

In summary, I think there are situations in which it is possible to generalize safety findings in preterm infants fed a preterm formula to term infants intended to be fed a term formula. On the other hand, I don't think such generalizations are possible in all situations. In other words, it is likely that a decision about the validity of such a generalization must be made for virtually every situation.

I hope my comments will be helpful to the Committee.

Sincerely,



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